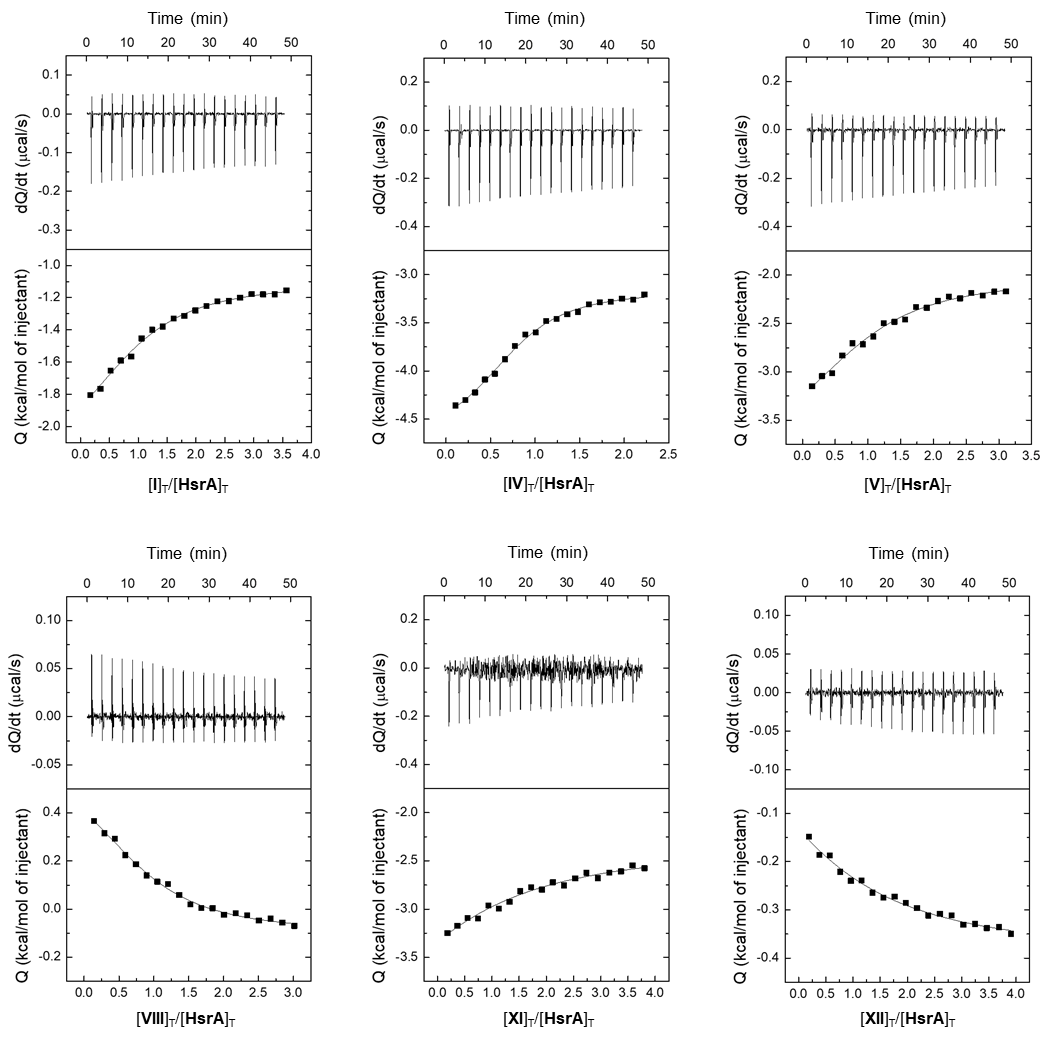
**Novel drug-like HsrA inhibitors exhibit potent narrow-spectrum antimicrobial activities against *Helicobacter pylori***

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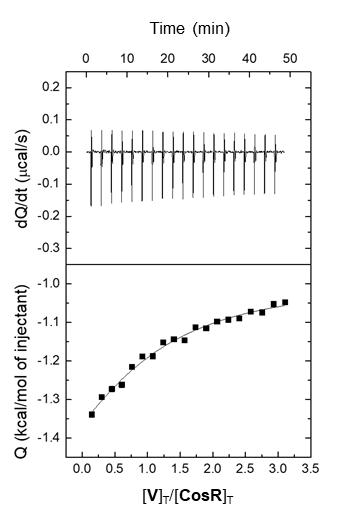
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**Figure S1.** Isothermal titration calorimetry (ITC) analyses of the interaction between the *H. pylori* response regulator HsrA and its low-molecular weight ligands I, IV, V, VIII, XI and XII. Thermograms of the protein interaction (thermal power as a function of time) with each ligand are depicted in the upper panel of the pictures, and the respective binding isotherms (titrant normalised heat effects as a function of the ligand:protein molar ratio in the cell) are showed in the lower panels.

|  |  |
| --- | --- |
| **Thermodynamic parameters** | |
| n | 0.9 |
| *K*d | 26 µM |
| Δ*H* | -0.9 kcal/mol |
| Δ*G* | -6.2 kcal/mol |



B

A

**Figure S2.** ITC analysis of the interaction between the *C. jejuni* response regulator CosR and compound V. **(A)** Upper panel shows the thermogram, while lower panel shows the binding isotherm. **(B)** Thermodynamics parameters of the interaction. Relative error in *K*d is 15%, absolute error in Δ*H* is 0.4 kcal/mol, absolute error in Δ*G* is 0.1 kcal/mol.

**Table S1**. Compounds from the Maybridge HitFinderTM chemical collection identified as HsrA ligands according the fluorescent thermal shift-based HTS.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ligand ID** | **Compound name** | **Maybridge Code** | **Δ*T*m**  **(ºC)**1 | **Molecular**  **formula** | **Molecular weight** | **ChemSpider ID** |
| I | 5-amino-1-[2-nitro-4-(trifluoromethyl)phenyl]-1H-pyrazole-4-carbonitrile | BTB02343 | 38 | C11H6F3N5O2 | 297.19 | 2076080 |
| II | 3-[(4-chlorophenyl)thio]-2-methyl-1H-indole | KM06044 | 20 | C15H12ClNS | 273.78 | 2099536 |
| III | 3-(4-fluorophenyl)-2-(1H-indol-3-yl)acrylonitrile | PD00112 | 17 | C17H11FN2 | 262.28 | 2104096 |
| IV | N-{2-[2,6-dinitro-4-(trifluoromethyl)anilino]ethyl}-N'-[3-(methylsulfanyl)phenyl]thiourea | CD03711 | 16 | C17H16F3N5O4S2 | 475.47 | 2082455 |
| V | N'-{[(4-chloroanilino)carbonyl]oxy}-5-nitrothiophene-3-carboximidamide | DFP00026 | 16 | C12H9ClN4O4S | 340.74 | 2084758 |
| VI | N'-({[3-(trifluoromethyl)anilino]carbonyl}oxy)-2,3-dihydro-1,4-benzodioxine-2-carboximidamide | KM06580 | 15 | C17H14F3N3O4 | 381.3 | 2099748 |
| VII | 2-methyl-4-{2-[3-(trifluoromethyl)phenyl]diaz-1-enyl}aniline | BTB06669 | 15 | C14H12F3N3 | 279.26 | 2078541 |
| VIII | 3-(10H-phenothiazin-2-yl)-5-(trifluoromethyl)-4,5-dihydro-1H-pyrazol-5-ol | SP01458 | 14 | C16H12F3N3OS | 351.35 | 2024533 |
| IX | 2-[3-(trifluoromethyl)-1H-pyrazol-1-yl]-N'-[({4-[(trifluoromethyl)thio]anilino}carbonyl)oxy]ethanimidamide | HAN00349 | 13 | C14H11F6N5O2S | 427.33 | 2087678 |
| X | 2-[2-(2-methyl-1-benzofuran-3-yl)acetyl]-N-[3-(trifluoromethyl)phenyl]-1-hydrazinecarbothioamide | FV00183 | 11 | C19H16F3N3O2S | 407.4 | 2086022 |
| XI | N2-[3-(methylthio)phenyl]-4-(tert-butyl)-1,3-thiazol-2-amine | BTB04902 | 11 | C14H18N2S2 | 278.44 | 2077472 |
| XII | 2-(1H-benzimidazol-2-yl)-5-phenylpenta-2,4-dienenitrile | PHG00723 | 9 | C18H13N3 | 271.32 | 606452 |
| XIII | 1-(5-isopropyl-3,8-dimethyl-1-azulenyl)-2-(4-methoxyphenyl)-1-diazene | SEW04851 | 9 | C22H24N2O | 332.44 | 17921592 |
| XIV | [1,1'-biphenyl]-4-yl(5-nitro-1-benzofuran-2-yl)methanol | RH01805 | 9 | C21H15NO4 | 345.35 | 2010255 |
| XV | 5-nitrothiophene-3-carbaldehyde N-(4-bromo-3-chlorophenyl)hydrazone | DFP00003 | 9 | C11H7BrClN3O2S | 360.61 | 7857708 |
| XVI | 1-(4-fluorophenyl)-5-methyl-N-{2-[2-nitro-4-(trifluoromethyl)anilino]ethyl}-1H-pyrazole-4-carboxamide | HTS05759 | 8 | C20H17F4N5O3 | 451.37 | 2091051 |
| XVII | ethyl 4-[5-(4-morpholinobuta-1,3-dienyl)-2H-1,2,3,4-tetraazol-2-yl]benzoate | BTB12773 | 8 | C18H21N5O3 | 355.39 | 4651038 |
| XVIII | 2-(4-chlorophenyl)-5-{[(4-pyridin-3-ylpyrimidin-2-yl)thio]methyl}-2,4-dihydro-3H-pyrazol-3-one | MWP01044 | 7 | C19H14ClN5OS | 395.87 | 2102650 |
| XIX | N1-(3-chlorophenyl)-2-{2-[(2-methyl-1H-indol-3-yl)thio]acetyl}hydrazine-1-carboxamide | KM07954 | 7 | C18H17ClN4O2S | 388.87 | 2100308 |
| XX | 4-amino-3,5-dichloro-N'-({[4-(trifluoromethoxy)anilino]carbonyl}oxy)benzenecarboximidamide | SEW03768 | 7 | C15H11Cl2F3N4O3 | 423.17 | 2022070 |
| XXI | 2-amino-6-(tert-pentyl)-4,5,6,7-tetrahydro-1-benzothiophene-3-carbonitrile | HTS05438 | 7 | C14H20N2S | 248.39 | 514469 |
| XXII | ethyl 1-[(3-chloroanilino)carbonyl]-4-(phenylthio)-1H-pyrazole-5-carboxylate | SPB03702 | 7 | C19H16ClN3O3S | 401.87 | 2026372 |
| XXIII | N-(1-methyl-3-phenyl-1H-pyrazol-5-yl)-N'-(2-thienyl)urea | HTS10230 | 7 | C15H14N4OS | 298.36 | 2093643 |
| XXIV | 13H-dibenzo[a,i]carbazole | JFD03891 | 7 | C20H13N | 267.32 | 8845 |
| XXV | N-(2-thienyl)-N'-{6-[3-(trifluoromethyl)phenoxy]-3-pyridinyl}urea | HTS08492 | 7 | C17H12F3N3O2S | 379.36 | 2092650 |
| XXVI | 2-({6-[(2-aminophenyl)sulfanyl]-5-nitro-2-pyridyl}sulfanyl)aniline | SEW05581 | 6 | C17H14N4O2S | 338.38 | 2022927 |
| XXVII | 2-acetyl-4-nitroindane-1,3-dione | JFD02083 | 6 | C11H7NO5 | 233.18 | 2016957 |
| XXVIII | N3-[4-(trifluoromethoxy)phenyl]-4-hydroxy-1,5,6-trimethyl-2,2-dioxo-1,2-dihydro-2lambda~6~-thieno[2,3-c][1,2]thiazine-3-carboxamide | KM04706 | 6 | C17H15F3N2O5S2 | 448.44 | 17926070 |
| XXIX | N-(5-cyclopropyl-1,3,4-thiadiazol-2-yl)-2-(2-fluorophenyl)acetamide | HTS02730 | 6 | C13H12FN3OS | 277.32 | 2089264 |
| XXX | N1-[5-(4-fluoroanilino)penta-2,4-dienylidene]-4-fluoroaniline hydrochloride | NRB00096 | 6 | C17H14F2N2.HCl | 320.76 | 4653283 |
| XXXI | N-[2-(4-chlorophenyl)-3-oxo-6-(2-thienylcarbonyl)-2,3-dihydro-4-pyridazinyl]acetamide | HTS08477 | 5 | C17H12ClN3O3S | 373.81 | 2092639 |

1Increase in the *T*m value of protein-ligand complex with respect to the mean *T*m value of controls (protein + DMSO).

**Table S3**. Functional classification of DEGs

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **ORF** | **Gene**  **name** | **Gene annotation**1 | **Fold Change** | **Effect** |
|  | | | |  |
| ***Ribosome biogenesis*** | | | |  |
| *hp0296* | *rplU* | 50S ribosomal protein L21 | -8,68 | down |
| *hp0125* | *rpmI* | 50S ribosomal protein L35 | -6,96 | down |
| *hp1320* | *rpsJ* | 30S ribosomal protein S10 | -6,14 | down |
| *hp0297* | *rpmA* | 50S ribosomal protein L27 | -5,89 | down |
| *hp0247* | *deaD* | ATP-dependent RNA helicase DeaD | -4,71 | down |
| *hp1297* | *rpmJ* | 50S ribosomal protein L36 | -4,58 | down |
| *hp0200* | *rpmF* | 50S ribosomal protein L32 | -4,52 | down |
| *hp1149* | *rimM* | 16S rRNA processing protein RimM | -4,26 | down |
| *hp1040* | *rpsO* | 30S ribosomal protein S15 | -4,08 | down |
| *hp0126* | *rplT* | 50S ribosomal protein L20 | -4,08 | down |
| *hp0491* | *rpmB* | 50S ribosomal subunit protein L28 | -3,87 | down |
| *hp1447* | *rpmH* | 50S ribosomal protein L34 | -3,68 | down |
| *hp1063* | *rsmG* | 16S rRNA methyltransferase | -3,33 | down |
| *hp1296* | *rpsM* | 30S ribosomal protein S13 | -3,25 | down |
| *hp1147* | *rplS* | 50S ribosomal protein L19 | -3,13 | down |
| *hp0084* | *rplM* | 50S ribosomal protein L13 | -3,07 | down |
| *hp1496* | *rplY* | 50S ribosomal protein L25 | -3,05 | down |
| *hp1151* | *rpsP* | 30S ribosomal protein S16 | -3,01 | down |
| *hp1200* | *rplJ* | 50S ribosomal subunit protein L10 | -2,95 | down |
| *hp1428* | *rlmM* | Ribosomal RNA large subunit methyltransferase N | -2,85 | down |
| *hp1303* | *rplR* | 50S ribosomal protein L18 | -2,67 | down |
| *hp1160* | *ybeY* | rRNA maturation factor | -2,56 | down |
| *hp0076* | *rpsT* | 30S ribosomal protein S20 | -2,53 | down |
| *hp1302* | *rpsE* | 30S ribosomal protein S5 | -2,47 | down |
| *hp0551* | *rpmE* | 50S ribosomal protein L31 | -2,47 | down |
| *hp0399* | *rpsA* | 30S ribosomal protein S1 | -2,45 | down |
| *hp0562* | *rpsU* | 30S ribosomal protein S21 | -2,34 | down |
| *hp1311* | *rpmC* | 50S ribosomal protein L29 | -2,25 | down |
| *hp1197* | *rpsL* | 30S ribosomal protein S12 | -2,20 | down |
| *hp1319* | *rplC* | 50S ribosomal protein L3 | -2,20 | down |
| *hp1295* | *rpsK* | 30S ribosomal protein S11 | -2,19 | down |
| *hp0553* | *rlmB* | 23S rRNA (guanosine(2251)-2'-O)-methyltransferase | -2,16 | down |
| *hp0956* | *rluC* | 23S rRNA pseudouridine synthase | -2,13 | down |
| *hp1068* | *prmA* | Ribosomal protein L11 methyltransferase | -2,10 | down |
| *hp1202* | *rplK* | 50S ribosomal protein L11 | -2,07 | down |
| *hp1309* | *rplN* | 50S ribosomal protein L14 | -2,01 | down |
| *hpr07* | *hprrnB16S* | 16S rRNA | 15,28 | up |
| *hpr01* | *hprrnA23S* | 23S rRNA | 8,08 | up |
| *hpr06* | *hprrnB23S* | 23S rRNA | 7,82 | up |
| *hpr04* | *hprrnA16S* | 16S rRNA | 6,23 | up |
| *hpr03* | *hprrnC5S* | 5S rRNA | 6,00 | up |
| *hpr02* | *hprrnA5S* | 5S rRNA | 5,86 | up |
| *hpr05* | *hprrnB5S* | 5S rRNA | 4,07 | up |
| *hp0569* | *ychF* | Ribosome-binding ATPase | 3,62 | up |
|  |  |  |  |  |
| ***Amino acid metabolism*** | | | |  |
| *hp0695* | *hyuA* | hydantoinase/oxoprolinase family protein | 4,96 | up |
| *hp0696* |  | N-methylhydantoinase | 4,92 | up |
| *hp0943* | *dadA* | D-amino-acid dehydrogenase | 4,73 | up |
| *hp0294* | *amiE* | aliphatic amidase | 3,23 | up |
| *hp1398* | *ald* | alanine dehydrogenase | 3,15 | up |
| *hp0723* | *ansB* | L - asparaginase II | 3,08 | up |
| *hp1210* | *cysE* | serine O-acetyltransferase | 2,95 | up |
| *hp0330* | *ilvC* | ketol-acid reductoisomerase | 2,90 | up |
| *hp0944* |  | 2-iminobutanoate/2-iminopropanoate deaminase | 2,82 | up |
| *hp0691* | *yxjD* | 3-oxoadipate coA-transferase subunit A | 2,80 | up |
| *hp1468* | *ilvE* | branched-chain amino acid aminotransferase | 2,76 | up |
| *hp0510* | *dapB* | 4-hydroxy-tetrahydrodipicolinate reductase | 2,74 | up |
| *hp0626* | *dapD* | tetrahydrodipicolinate N-succinyltransferase | 2,63 | up |
| *hp0020* | *nspC* | carboxynorspermidine decarboxylase | 2,61 | up |
| *hp0692* | *yxjE* | 3-oxoadipate coA-transferase subunit B | 2,51 | up |
| *hp0649* | *aspA* | aspartate ammonia-lyase | 2,42 | up |
| *hp0056* |  | delta-1-pyrroline-5-carboxylate dehydrogenase | 2,24 | up |
| *hp0134* | *dhs1* | 3-deoxy-7-phosphoheptulonate synthase | 2,22 | up |
| *hp0096* |  | phosphoglycerate dehydrogenase | 2,17 | up |
| *hp0663* | *aroC* | chorismate synthase | 2,16 | up |
| *hp1050* | *thrB* | homoserine kinase | 2,12 | up |
| *hp0132* | *sdaA* | L-serine deaminase | 2,12 | up |
| *hp0357* |  | 3-hydroxy acid dehydrogenase / malonic semialdehyde reductase | 2,04 | up |
| *hp0380* | *gdhA* | Glutamate dehydrogenase | 2,03 | up |
| *hp0098* | *thrC* | threonine synthase | -2,31 | down |
| *hp1282* | *trpE* | anthranilate synthase component I | -2,12 | down |
| *hp0307* | *argJ* | Arginine biosynthesis bifunctional protein ArgJ | -2,11 | down |
|  |  |  |  |  |
| ***Carbon metabolism*** | | | |  |
| *hp0779* | *acnB* | aconitase B | 4,11 | up |
| *hp1100* | *edd* | phosphogluconate dehydratase | 4,07 | up |
| *hp1099* | *eda* | bifunctional 4-hydroxy-2-oxoglutarate aldolase/2-dehydro-3-deoxy-phosphogluconate aldolase | 3,73 | up |
| *hp0697* |  | acetone carboxylase, gamma subunit | 3,43 | up |
| *hp1045* | *acoE* | acetyl-CoA synthetase | 3,11 | up |
| *hp1103* | *glk* | glucokinase | 2,83 | up |
| *hp1101* | *zwf* | glucose-6-phosphate dehydrogenase | 2,82 | up |
| *hp1166* | *pgi* | glucose-6-phosphate isomerase | 2,68 | up |
| *hp1102* | *devB* | 6-phosphogluconolactonase | 2,50 | up |
| *hp1345* | *pgk* | phosphoglycerate kinase | 2,12 | up |
| *hp1104* |  | (NADP+)-dependent alcohol dehydrogenase | 2,12 | up |
| *hp0574* | *lacA* | ribose 5-phosphate isomerase B | -4,10 | down |
| *hp0588* | *oorD* | 2-oxoglutarate ferredoxin oxidoreductase, subunit delta | -3,05 | down |
|  |  |  |  |  |
| ***Lipid metabolism*** | | | |  |
| *hp0557* | *accA* | acetyl-CoA carboxylase carboxyl transferase subunit alpha | -2,66 | down |
| *hp1016* | *pgsA* | phosphatidylglycerophosphate synthase | -2,66 | down |
| *hp0371* | *accB* | acetyl-CoA carboxylase biotin carboxyl carrier protein | -2,25 | down |
| *hp1348* | *plsC* | 1-acyl-glycerol-3-phosphate acyltransferase | -2,24 | down |
| *hp0559* | *acpP* | acyl carrier protein | -2,23 | down |
| *hp0700* | *dgkA* | diacylglycerol kinase | -2,20 | down |
| *hp0561* | *fabG* | 3-ketoacyl-acyl carrier protein reductase | -2,11 | down |
| *hp0871* | *cdh* | CDP-diacylglycerol diphosphatase | 5,77 | up |
| *hp0090* | *fabD* | ACP S-malonyltransferase | 2,68 | up |
| *hp0690* | *fadA* | acetyl-CoA acetyltransferase (thiolase) | 2,25 | up |
|  |  |  |  |  |
| ***Transporters*** | | | |  |
| *hp1174* | *gluP* | glucose/galactose transporter | 4,11 | up |
| *hp0715* | *lptB* | LPS export ABC transporter ATP-binding protein | 3,38 | up |
| *hp0133* | *sdaC* | HAAAP family serine/threonine permease | 2,92 | up |
| *hp0251* | *oppC* | oligopeptide ABC transporter permease | 2,89 | up |
| *hp0759* |  | MATE family efflux transporter | 2,55 | up |
| *hp0613* |  | ABC transporter ATP-binding protein | 2,51 | up |
| *hp1180* | *nupC* | bacterial concentrative nucleoside transporter | 2,40 | up |
| *hp0942* | *dagA* | D-alanine glycine permease | 2,35 | up |
| *hp1168* | *cstA* | carbon starvation protein A | 2,31 | up |
| *hp1290* | *pnuC* | nicotinamide riboside transporter PnuC | 2,30 | up |
| *hp0140* | *lctP* | L-lactate permease | 2,28 | up |
| *hp0983* |  | small conductance mechanosensitive channel | 2,25 | up |
| *hp0693* |  | short-chain fatty acids transporter | 2,23 | up |
| *hp1400* | *fecA* | Fe3+ dicitrate transport protein (fecA) | 2,15 | up |
| *hp0818* | *proWX* | Osmoprotectant ABC transporter permease | 2,14 | up |
| *hp0724* | *dcuA* | anaerobic C4-dicarboxylate transporter | 2,13 | up |
| *hp0686* | *fecA* | Fe3+ dicitrate transport protein | 2,03 | up |
| *hp0490* | *hpkchA* | voltage-gated potassium channel | -3,42 | down |
| *hp0582* | *tonB1* | Periplasmic protein TonB | -2,67 | down |
| *hp1498* |  | LPS export system permease protein | -2,54 | down |
| *hp0687* | *feoB* | ferrous iron transport protein B | -2,48 | down |
| *hp0229* | *hopA* | outer membrane porin HopA | -2,40 | down |
| *hp1486* |  | ABC transporter permease | -2,19 | down |
| *hp1341* | *tonB2* | Periplasmic protein TonB | -2,15 | down |
|  |  |  |  |  |
| ***Virulence*** | | | |  |
| *hp0439* |  | Bacterial virulence protein VirB8 domain-containing protein | 4,92 | up |
| *hp0310* | *pgdA* | peptidoglycan-N-acetylglucosamine deacetylase | 4,68 | up |
| *hp0547* | *cagA* | Type IV secretion system oncogenic effector CagA | 3,78 | up |
| *hp0017* | *virB4a* | VirB4 family type IV secretion/conjugal transfer ATPase | 3,68 | up |
| *hp0751* | *flaG* | polar flagellin FlaG | 3,16 | up |
| *hp0752* | *fliD* | flagellar hook-associated protein 2 | 2,30 | up |
| *hp0520* | *cag1* | cag pathogenicity island protein Cag1 | 2,97 | up |
| *hp0019* | *cheV1* | chemotaxis protein CheV1 | 2,88 | up |
| *hp1238* | *amiF* | formamidase | 2,65 | up |
| *hp1243* | *babA* | Hop family adhesin BabA | 2,55 | up |
| *hp0541* | *cag20* | cag pathogenicity island protein Cag20 | 2,40 | up |
| *hp0243* | *napA* | neutrophil-activating protein NapA | 2,35 | up |
| *hp0896* | *babB* | Hop family adhesin BabB | 2,24 | up |
| *hp0601* | *flaA* | flagellin A | 2,16 | up |
| *hp1399* | *rocf* | arginase | 2,12 | up |
| *hp1086* | *tlya* | hemolysin | 2,07 | up |
| *hp0542* | *cag21* | cag pathogenicity island protein Cag21 | 2,05 | up |
| *hp1186* |  | carbonic anhydrase | 2,04 | up |
| *hp1052* | *envA* | UDP-3-O-acyl-N-acetylglucosamine deacetylase | 2,02 | up |
| *hp0069* | *ureF* | urease accessory protein UreF | -4,03 | down |
| *hp0725* | *sabA* | Hop family adhesin SabA | -3,26 | down |
| *hp1203a* | *secE* | preprotein translocase subunit SecE | -3,12 | down |
| *hp0546a* | *picA* | cag pathogenicity island protein | -3,01 | down |
| *hp0068* | *ureG* | urease accessory protein UreG | -2,89 | down |
| *hp1039* |  | O-antigen ligase | -2,76 | down |
| *hp0492* |  | neuraminyllactose-binding hemagglutinin | -2,56 | down |
| *hp0855* | *algl* | alginate O-acetyltransferase complex protein A | -2,55 | down |
| *hp0327* | *pseH* | UDP-4-amino-4,6-dideoxy-N-acetyl-beta-L-altrosamine N-acetyltransferase | -2,53 | down |
| *hp0544* | *cag23* | cag pathogenicity island type IV secretion system ATPase CagE | -2,51 | down |
| *hp1578* |  | α-(1,2)-N-acetylglucosyltransferase | -2,48 | down |
| *hp0280* | *lpxL* | lipid A biosynthesis lauroyl acyltransferase | -2,29 | down |
| *hp1274* | *pflA* | paralysed flagella protein | -2,27 | down |
| *hp0508* | *pgbA* | plasminogen-binding protein PgbA | -2,24 | down |
| *hp1034* | *ylxH* | flagellar biosynthesis protein FlhG | -2,20 | down |
| *hp0526* | *cag6* | cag pathogenicity island translocation protein CagZ | -2,18 | down |
| *hp0244* | *flgS* | acid survival sensor histidine kinase | -2,18 | down |
| *hp0190* | *clsC* | Cardiolipin synthase | -2,16 | down |
| *hp0410* | *hpaA2* | neuraminyllactose-binding hemagglutinin | -2,10 | down |
| *hp0256* | *fliJ* | flagellar export protein FliJ | -2,10 | down |
| *hp0523* | *cag4* | cag pathogenicity island protein (cag4) | -2,10 | down |
| *hp1006* | *virD4* | Type IV secretion system protein VirD4 | -2,10 | down |
| *hp1462* |  | flagellar motility protein | -2,04 | down |
|  |  |  |  |  |
| ***Chaperones and heat shock proteins*** | | | |  |
| *hp0109* | *dnaK* | molecular chaperone DnaK | 3,26 | up |
| *hp0264* | *clpB* | ATP-dependent Clp protease ATP-binding subunit ClpB | 3,23 | up |
| *hp0110* | *grpE* | nucleotide exchange factor GrpE | 3,22 | up |
| *hp0010* | *groEL* | chaperonin GroEL | 2,74 | up |
| *hp1024* | *cbpA* | co-chaperone-curved DNA binding protein A | 2,67 | up |
| *hp0210* | *htpG* | molecular chaperone HtpG | 2,04 | up |
|  |  |  |  |  |
| ***tRNA biosynthesis*** | | | |  |
| *hpt28* | *tRNA-Met-1* | Transfer RNA | 4,41 | up |
| *hpt09* | *tRNA-Ala-1* | Transfer RNA | 3,71 | up |
| *hpt20* | *tRNA-Met-3* | Transfer RNA | 3,67 | up |
| *hpt34* | *tRNA-Leu-2* | Transfer RNA | 3,53 | up |
| *hpt35* | *tRNA-Leu-3* | Transfer RNA | 3,15 | up |
| *hpt17* | *tRNA-Arg-3* | Transfer RNA | 2,86 | up |
| *hpt02* | *tRNA-Asp-1* | Transfer RNA | 2,74 | up |
| *hpt10* | *tRNA-Arg-1* | Transfer RNA | 2,72 | up |
| *hpt01* | *tRNA-Glu-1* | Transfer RNA | 2,71 | up |
| *hpt08* | *tRNA-Asn-1* | Transfer RNA | 2,67 | up |
| *hpt26* | *tRNA-Pro-1* | Transfer RNA | 2,67 | up |
| *hpt27* | *tRNA-Ser-2* | Transfer RNA | 2,58 | up |
| *hpt21* | *tRNA-Gln-1* | Transfer RNA | 2,51 | up |
| *hpt31* | *tRNA-Gly-2* | Transfer RNA | 2,40 | up |
| *hpt11* | *tRNA-Ala-2* | Transfer RNA | 2,23 | up |
| *hpt18* | *tRNA-Met-2* | Transfer RNA | 2,16 | up |
| *hpt15* | *tRNA-His-1* | Transfer RNA | 2,12 | up |
| *hp0774* | *tyrS* | tyrosyl-tRNA synthetase | 2,06 | up |
| *hp0830* | *gatA* | Glu-tRNA(Gln) amidotransferase, subunit A | 2,04 | up |
| *hp1241* | *alaS* | alanyl-tRNA synthetase | 2,00 | up |
| *hp1448* | *rnpA* | ribonuclease P protein component | -2,92 | down |
| *hp1148* | *trmD* | tRNA (guanine-N1)-methyltransferase | -2,51 | down |
| *hp1452* | *mnmE* | tRNA modification GTPase | -2,28 | down |
| *hp0182* | *lysS* | lysyl-tRNA synthetase | -2,08 | down |
|  |  |  |  |  |
| ***Vitamins, secondary metabolites, and cofactors*** | | | |  |
| *hp1291* |  | thiamine diphosphokinase | 4,40 | up |
| *hp0006* | *panC* | pantoate--beta-alanine ligase | 2,53 | up |
| *hp0845* | *thiM* | hydroxyethylthiazole kinase | 2,45 | up |
| *hp0844* | *thi* | bifunctional hydroxymethylpyrimidine kinase/phosphomethylpyrimidine kinase | 2,29 | up |
| *hp0034* | *panD* | aspartate 1-decarboxylase | 2,05 | up |
| *hp0761* |  | 5-formyltetrahydrofolate cyclo-ligase | 2,01 | up |
| *hp1545* | *folC* | bifunctional folylpolyglutamate synthase/dihydrofolate synthase | -2,90 | down |
| *hp1224* | *hemD* | Uroporphyrinogen-III synthase | -2,23 | down |
| *hp0934* | *queE* | 7-carboxy-7-deazaguanine synthase | -2,13 | down |
| *hp0769* | *mobA* | molybdenum cofactor guanylyltransferase MobA | -2,04 | down |
|  |  |  |  |  |
| ***Metal resistance*** | | | |  |
| *hp1073* | *copP* | copper-binding metallochaperone CopP | -2,57 | down |
| *hp1488* |  | efflux RND transporter periplasmic adaptor subunit | -2,27 | down |
| *hp1072* | *copA* | Cu2+ exporting P-type ATPase CopA | -2,14 | down |
| *hp0971* | *cznC* | Ni2+/Zn2+/Cd2+ efflux pump, outer membrane channel | -2,13 | down |
| *hp0653* | *pfr* | ferritin | 4,73 | up |
| *hp1326* | *crdA* | copper resistance determinant CrdA | 2,05 | up |
|  |  |  |  |  |
| ***Electron transfer and oxidative phosphorylation*** | | | |  |
| *hp0377* | *resA* | dithiol reductase/isomerase ResA | -2,58 | down |
| *hp1137* | *atpX* | F0F1 ATP synthase, subunit B´ | -2,43 | down |
| *hp0378* | *ccsbA* | bifunctional cytochrome c biogenesis protein CcsBA | -2,26 | down |
| *hp1135* | *atpH* | F0F1 ATP synthase, subunit D | -2,23 | down |
| *hp0828* | *atpB* | F0F1 ATP synthase, subunit A | -2,12 | down |
| *hp1227* | *cyt553* | cytochrome c-553 | -2,07 | down |
| *hp1273* | *nuoN* | NADH-quinone oxidoreductase subunit NuoN | -2,04 | down |
| *hp1136* | *atpF* | F0F1 ATP synthase, subunit B | -2,03 | down |
| *hp0193* | *frdC* | fumarate reductase, cytochrome b subunit | -2,01 | down |
| *hp0631* | *hydA* | Quinone-reactive Ni/Fe hydrogenase | 4,06 | up |
| *hp0632* | *hydB* | Quinone-reactive Ni/Fe hydrogenase | 3,66 | up |
| *hp0633* | *hydC* | Ni/Fe-hydrogenase, b-type cytochrome subunit | 3,08 | up |
|  |  |  |  |  |
| ***Restriction and modification systems*** | | | |  |
| *hp1402* | *hsdR3* | Type I restriction endonuclease subunit R | 4,51 | up |
| *hp0262* |  | Type II restriction enzyme | 2,90 | up |
| *hp1208* |  | adenine-specific DNA-methyltransferase | 2,30 | up |
| *hp0091* | *hsdR* | Type II restriction endonuclease | 2,13 | up |
| *hp1517* |  | DNA methyltransferase | 2,09 | up |
| *hp1403* | *hsdM* | Type I restriction enzyme M protein | 2,05 | up |
| *hp0592* | *hpyAXIR* | Type III restriction-modification system endonuclease | -3,44 | down |
| *hp0050* | *dpnA* | adenine specific DNA-methyltransferase | -2,05 | down |
|  |  |  |  |  |
| ***Replication, repair, recombination*** | | | |  |
| *hp1460* | *dnaE* | DNA polymerase III subunit alpha | 3,18 | up |
| *hp1470* | *polA* | DNA polymerase I | 2,48 | up |
| *hp0438* | *tnpB* | transposase | 2,14 | up |
| *hp1114* | *uvrB* | excinuclease ABC subunit B (UvrB) | 2,04 | up |
| *hp0827* |  | Single-strand DNA-binding protein (SSB) | -5,38 | down |
| *hp1231* | *holB* | DNA polymerase III subunit delta | -2,96 | down |
| *hp1347* | *ung* | uracil-DNA glycosylase | -2,30 | down |
|  | | | |  |
| ***Translation factors*** | | | |  |
| *hp0077* | *prfA* | peptide chain release factor 1 | -6,12 | down |
| *hp1298* | *infA* | translation initiation factor IF-1 | -4,62 | down |
| *hp1441* | *ppiA* | peptidyl-prolyl cis-trans isomerase B | -3,06 | down |
| *hp0795* | *tig* | trigger factor | -2,49 | down |
| *hp1497* | *pth* | peptidyl-tRNA hydrolase | -2,21 | down |
| *hp1123* | *slyD* | peptidyl-prolyl cis-trans isomerase | -2,09 | down |
| *hp0124* | *infC* | translation initiation factor IF-3 | -2,02 | down |
|  |  |  |  |  |
| ***Transcription factors*** | | | |  |
| *hp1025* | *hspR* | MerR family transcriptional regulator HspR | 3,79 | up |
| *hp0111* | *hrcA* | HrcA family transcriptional regulator | 3,47 | up |
| *hp0714* | *rpoN* | RNA polymerase factor sigma-54 | 2,06 | up |
| *hp0866* | *greA* | transcription elongation factor GreA | 2,01 | up |
| *hp1203* | *nusG* | transcription termination factor NusG | -2,36 | down |
| *hp0550* | *rho* | transcription termination factor Rho | -2,26 | down |
|  |  |  |  |  |
| ***Outer membrane proteins*** | | | |  |
| *hp1342* | *hopN* | Hop family outer membrane protein HopN | 3,16 | up |
| *hp0227* | *hopM* | Hop family outer membrane protein HopM | 3,09 | up |
| *hp0317* | *omp9* | outer membrane beta-barrel protein | 2,73 | up |
| *hp0472* | *omp11* | outer membrane beta-barrel protein | 2,46 | up |
| *hp1395* | *horL* | outer membrane protein HorL/Omp30 | 2,22 | up |
| *hp1456* | *lpp20* | LPP20 family lipoprotein | 2,16 | up |
| *hp1066* |  | Outer membrane protein | 2,08 | up |
|  |  |  |  |  |
| ***Antioxidant enzymes*** | | | |  |
| *hp0875* | *katA* | catalase | 3,11 | up |
| *hp0389* | *sodB* | superoxide dismutase [Fe] | 2,43 | up |
| *hp1461* | *ccP* | cytochrome c551 peroxidase | 2,32 | up |
| *hp0407* | *bisC* | Biotin sulfoxide reductase | 2,10 | up |
|  |  |  |  |  |
| ***Nucleotide metabolism*** | | | |  |
| *hp1218a* | *purD* | glycinamide ribonucleotide synthetase | 5,94 | up |
| *hp1240* |  | nucleoside triphosphate pyrophosphatase | 3,11 | up |
| *hp1178* | *deoD* | purine-nucleoside phosphorylase | 2,38 | up |
| *hp0735* | *gpt* | xanthine guanine phosphoribosyl transferase | -2,28 | down |
|  |  |  |  |  |
| ***Peptidases*** | | | |  |
| *hp1069* | *ftsH* | ATP-dependent zinc metalloprotease FtsH | 3,77 | up |
| *hp0570* | *pepA* | leucyl aminopeptidase | 3,65 | up |
| *hp1299* | *map* | methionine amino peptidase | -2,04 | down |
|  |  |  |  |  |
| ***Others*** | | | |  |
| *hp1450* | *yidC* | YidC/Oxa1 family membrane protein insertase | -3,72 | down |
| *hp0645* | *slt* | peptidoglycan lytic transglycosylase | -3,36 | down |
| *hp0331* | *minD* | septum site-determining protein MinD | 2,15 | up |
| *hp1198* | *rpoB* | DNA-directed RNA polymerase, beta subunit | 2,01 | up |

1Gene annotations and functional categories were assigned according to the information stored in the databases KEEG (https://www.genome.jp/kegg/), BioCyc (https://biocyc.org/), and UniProt (https://www.uniprot.org/).

**Table S4.** List of oligonucleotides used in this study.

|  |  |  |
| --- | --- | --- |
| **Oligo ID** | **Sequence 5´- 3´** | **Use** |
| HsrA\_up | GGAATTCCATATGCGCGTTCTACTGATTG | Cloning *hsrA* |
| HsrA\_dw | CCCAAGCTTTTACTCTTCACACGCCGG | Cloning *hsrA* |
| CosR\_up | GGAATTCCATATGAGAATTTTAGTTATAGAAG | Cloning *cosR* |
| CosR\_dw | CGGGATCCTTAAGATTTTTTAGGGAAGCAGAAACGG | Cloning *cosR* |
| PporG\_up | CCCCACACTTGCCCCATACAGAC | EMSA |
| PporG\_dw | GCATGCCATCTAATTTGAAACATGG | EMSA |
| PsodB\_up | CTGCGAAAGCACCTAGTAATGC | EMSA |
| PsodB\_dw | GTAACATAAGTATTGTGATGTTTTCCATG | EMSA |
| pkn22\_up | CGGTCAAGCTGTACAGCAGTCAG | EMSA |
| pkn22\_dw | GAACGCCATAGCCTACAGTAGGC | EMSA |
| qPCR-glnAup | CGGATGTGAGCGTGGTCGTG | qPCR |
| qPCR-glnAdw | GCCACATCGCCCAAACCTGAATC | qPCR |
| qPCR-rpmIup | CGGCGCGTCTAAGCGTTTCAAAG | qPCR |
| qPCR-rpmIdw | CGCGTTTAGATTGGCTTTGCGC | qPCR |
| qPCR-tlpBup | GAGCATGAAAGATTCCTCAACCACC | qPCR |
| qPCR-tlpBdw | CGTTTCAATCAAACGCTTCCTTAACC | qPCR |
| qPCR-rplUup | GGAAGTGTTAGCCGTATCCAAAGAGGG | qPCR |
| qPCR-rplUdw | GCCGCGCCCTTCATTGATCAC | qPCR |
| qPCR-rpmAup | GATTCTGCAGGAAGACGCTTAGGCG | qPCR |
| qPCR-rpmAdw | CCCATGCCCACATTATTACCAGGATGC | qPCR |
| qPCR-sodBup | GCGACTGCCCTAAGCGATGAG | qPCR |
| qPCR-sodBdw | GTGGTCGCGCTCTTAATGAAGTC | qPCR |
| qPCR-16SRNAup | CTGAGAGGGTGAACGGACACACTG | qPCR |
| qPCR-16SRNAdw | CGTTGCTGCTTCAGGGTTTCCC | qPCR |
| qPCR-dnaEup | CAGCGCCGGCGTAAGGAAATC | qPCR |
| qPCR-dnaEdw | CTTGCGACATCTCTGATCACGCC | qPCR |
| qPCR-cagAup | CGGCAGTGGCTTAGTCATAGCAGG | qPCR |
| qPCR-cagAdw | GACTCAATGCTCGTTGTGAGCCTG | qPCR |
| qPCR-pfr-up | GCTTAGATGGCGCGGGGC | qPCR |
| qPCR-pfr-dw | GATGCTAGTCAATTGCACAGGCACATTG | qPCR |
| qPCR-cdh-up | GACTATGGCTTAGCGGTGGTGC | qPCR |
| qPCR-cdh-dw | GAATCTCTTCGGCTGAAGCGCG | qPCR |